INSULIN-GLUCOSE CLAMP FOR STANDARDIZATION OF METABOLIC CONDITIONS DURING F-18 FLUORO-DEOXYGLUCOSE PET IMAGING.

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Myocardial glucose utilization (MGU) can be quantitatively evaluated using Patlak graphic analysis of myocardial and blood pool F-18 fluoro-deoxyglucose (FDG) kinetics. Since MGU is regulated by substrate availability and hormonal status, we compared MGU following oral glucose loading (OG), as widely used for clinical PET FDG studies, with MGU during rigorous control of metabolic conditions with hyperinsulinemic-euglycemic clamping (CLAMP). Dynamic PET imaging with FDG was performed for 60 minutes, starting 30 minutes after OG (50 g Glucola) in 10 patients (Pts) without history of diabetes mellitus. Seven normal volunteers (NORMALS) and three patients with insulin-dependent diabetes mellitus (IDDM) were studied during CLAMP. All subjects were considered to have a low likelihood of coronary artery disease (CAD). In each study, global MGU was determined by averaged data from Patlak analysis of 60 sectors within each of 7-12 short-axis cardiac planes. Myocardial to blood pool activity ratios (M:B ratios) were determined at the end of dynamic PET imaging. Mean and standard deviation data are presented for each study population;

Protocol	Plasma Glucose	Global MGU	M:B Ratio
OG-Pts	107±28†	0.41±0.15	4.1±1.4†
CLAMP-NORMALS	85±7	0.47±0.09	6.8±2.5
CLAMP-IDDM	87±4	0.40±0.04	9.9±4.5

† p<0.05 compared with CLAMP-NORMALS and CLAMP-IDDM.

There was no statistically significant difference in MGU between patients studied following OG and normal subjects studied during CLAMP. However, less variability in MGU and improved M:B ratios were observed following CLAMP, providing enhanced image quality due to greater blood pool clearance of FDG activity. More importantly, CLAMP was associated with similar MGU in patients with IDDM, a sub-group known to have a high prevalence of technically sub-optimal FDG studies following OG.

In conclusion, CLAMP optimizes FDG image quality in both non-diabetic and IDDM patients and, by standardizing metabolic conditions, may be a valuable technique for use in combination with clinical PET imaging studies.

PREDICTION OF THE RECOVERY OF ASYNERGIC MYOCARDIUM FOLLOWING SUCCESSFUL THROMBOLYSIS USING O-15 WATER AND POSITRON EMISSION TOMOGRAPHY (PET)

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To predict the contractile recovery of asynergic myocardium, we studied 11 patients with acute myocardial infarction 3-6 days after successful thrombolysis using O-15 water, PET and echocardiography. Follow-up echocardiography was performed 4-6 months later to assess subsequent contractile recovery. Regional myocardial blood flow (MBF: ml/min/g of O-15 water perfusible tissue [PT]) was obtained from the PET data by a previously validated method, which corrects for partial volume effec . In addition to MBF, the O-15 water perfusible tissue content for each region of interest (ROI) (PTC: g of PT/ml of ROI) was estimated. Furthermore, it has been shown that extravascular tissue density (D: g of total {anatomical} tissue [PT + non-PT]/ml of ROI) can be obtained from the image produced by subtracting blood volume ($C^{15}O$) from a normalized transmission scan. Thus, the ratio PTC/D for a given ROI indicates the O-15 water perfusible fraction of the total tissue (PTC/D: g of PT/g of total tissue [PT + non-PT]). These parameters were estimated in 4 anatomical segments in each patient. The myocardial ROI's analyzed were grouped into 3 categories according to the wall motion pattern : 9 recovery segments (an average 5.6 fold increase in wall thickening); 5 non-recovery segments; and 11 remote control segments. Results are shown as mean±sd.

	NON-RECOVERY	RECOVERY	CONTROL
PTC/D	0.51±0.10*	0.88±0.09	0.97±0.10
MBF	0.60±0.18	0.68±0.29	1.01±0.21

It is reasonable that PTC/D in control segments was close to 1 because all normal myocardium should be perfusible by water over the short time duration of the O-15 water scan (7 minutes). PTC/D in recovery segments was significantly greater (*p<0.01) than in non-recovery segments whereas MBF was not statistically different in the two categories. Thus, the O-15 water perfusible fraction of the total tissue, but not MBF, may reveal the extent of myocardial salvage and enable the prediction of the potential recovery of asynergic myocardium following successful thrombolysis.

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Poster Displayed: 9:00AM–12:00NOON
Author Present: 10:00AM–11:00AM
Hall F, West Concourse
Myocarditis/Dilated Cardiomyopathy/Pericardial Disease

CHARACTERIZATION OF CYTOTOXIC AUTOANTIBODIES REACTING WITH A CYTOTOXIC/SUPPRESSOR T-LYMPHOCYTE SUBSET IN MYOCARDITIS

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Determination of functional characteristics and specificity of T-lymphocytes provides an opportunity to obtain insight into the histiology, pathogenesis and natural history of myocarditis. Recently we have characterized autoantibodies in sera of 20 patients with myocarditis showing an acute cytotoxic effect on human T-lymphocytes. This antibody mediated cytotoxic effect is calcium dependent. Binding of antibodies is correlated with a sudden increase in intracellular calcium concentration. Decreasing the extracellular calcium concentration or addition of calcium channel blockers such as Nifidipin, Nitrendipin or Verapamil (10^{-6}M) markdly reduced antibody-mediated cell death. For further characterization of the antibody binding site, human T-lymphocytes were seperated into their CD4- and CD8 positive subtypes using specific immunomagnetic antibodies to helper inducer and cytotoxic suppressor cells. Immunofluorescent staining revealed that patient sera do not react with helper/inducer cells but bind to a small lymphocyte subpopulation (15-25 %) of the CD8 positive cytotoxic-suppressor compartment. Positive cells represent 8-15 % of total peripheral blood lymphocytes. Our data indicate that these lymphocytes are not detected in sera of patients with acute onset of myocarditis showing high titers of cytotoxic autoantibodies. The lymphocytes however will recover at a later stage of the disease. Conclusion: These lymphocyte cytotoxic autoantibodies might eliminate antigen-specific suppressor cell clones and thus might be involved in the onset of the autoimmunological process in myocarditis.

THE ROLE OF T LYMPHOCYTES IN MYOSIN-INDUCED MYOCARDITIS

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Myocarditis can be caused by a variety of pathogens, and if progressive, can result in dilated cardiomyopathy and congestive heart failure. However, the stimulus and effector cells for this ongoing inflammation remain unclear. In these studies, we explore the role of the T cell in myocarditis using a model of autoimmune myocarditis. We can induce a mononuclear cell infiltrate and necrosis effecting greater than 40% of the myocardium by immunizing A/J mice with purified mouse cardiac myosin. These animals develop high antibody titers to cardiac myosin, but this antisera does not transfer myocarditis to syngeneic recipients suggesting that antibodies are not central in causing myocardial inflammation. However, blocking antigen presentation via the class II pathway with IE^k and IA^k-specific antagonist peptides effectively prevents myocarditis in greater than 95% of the immunized animals. In addition, treatment with monoclonal antibodies against the T cell accessory molecule CD4, also prevents myocarditis in the immunized mice. Eliminating myocarditis with peptides that block the effective interaction of CD4+ T cells with class II-bearing antigen presenting cells (apc), and with antibodies that prevent functional interaction of CD4+ T cells with apc's, argues strongly that the T lymphocyte is the immune effector cell causing induction and progression of myocarditis in this model system. Additional studies will address the immunogenic epitopes on cardiac myosin, why these animals can be rendered intolerant to cardiac myosin, and the molecular basis for the cardiac response to immune injury.